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Studies on the pharmacology of quarternary tropeines and β-amino-ketones.

Almost a century ago, in 1868, Brown and Fraser conducted their first successful experiments in the field of structure-activity relationships. They demonstrated that the pharmacological actions of alkaloids can be altered by methyl quarternization of the tertiary N-atom. This chemical change, that is the formation of an ammonium ion resulted in a loss of central stimulant or depressant actions of these alkaloids. On the other hand, it brought about curare-like actions on the motor-end-plates. These findings were first utilized 46 years ago when the need arose to broaden the therapeutic usefulness of atropine and homatropine. We found that the methylquaternary derivative of homatropine, which has become known in Hungary by the name of novatropine, and in this country as mesopin, had smaller toxicity and greater potency at the parasympathetic effector sites than the parent compound, homatropine. Another early observation of ours was also one of the first discovery in this field when a synergism between papaverine and parasympatholytic drugs was established. A combination preparation - Troparin - resulting from these studies, thus became the predecessor of hundreds of similar preparations. No further studies were made following these early investigations for about three decades - until 1942. Then, Griffith and Johnson, by introducing curare as an adjuvant of surgical anesthesia, initiated the search for developing synthetic curare agents. At that time, it occurred to me that the quarternary methyl-homatropinium salt (novatropin) also had some mild curare like properties. At my suggestion, Dr. Nador, a very excellent

organic chemist, ~~in my department~~, undertook a program, commencing in 1948, of synthesizing new quarternary ammonium compounds. On the basis of the observations of Barlow and Ing ~~for~~ in order to obtaining high curare-like potency, it was indicated that two quarternary ammonium groups should be present in the molecules about 15 Å apart from each other. Nador and his coworkers first produced compounds in which two quarternary ammonium groups were linked by diphenylmethane or by p-xylylene groups. Although the p-xylylene quarternary derivative of homatropine proved to have high curare-like activity, it was not suitable for therapeutic purposes because of its marked atropine-like action. ~~However~~ Nevertheless, this latter action could almost be completely eliminated by substituting the mandelic acid part of the molecule by benzoic acid. The resulting 1-4 xylylene, bis,α-benzoyloxy-tropinium bromide was found to be equipotent with tubocurarine and also had the advantage of being readily reversible by neostigmine. Later, Nador and Gyermek demonstrated that molecules with two tropine rings connected by dicarbonic acids, such as succinic and phtalic ~~xx~~ acids and quaternized with suitable aromatic groups also yield very potent curare like agents. Two of them (N-306 and 307) proved to be 2-5 times more potent than tubocurarine but besides their curare like action they also produced decreased considerable blood pressure ~~fall~~ by inhibiting ganglionic transmission.

Investigations of Fodor and Nador disclosed the stereochemical features of tropine compounds. With the use of the N-O acyl migration reaction they determined the configuration of tropine and pseudotropine demonstrating that in the tropine molecule the 3-OH

group has an anti (α) position whereas in the pseudotropine it has a syn (β) position. Nador has synthesized several stereoisomeric pairs of bisquarternary tropeines. Their pharmacological studies showed that the curare-like action of tropine derivatives is much superior to that of the pseudotropines. However, it soon became apparent that the curare-like action was even more dependent on the constellation around the N atom. Fodor discovered that the N-CH_3 group of the tropine ring is directed toward the C_3-OH group of the molecule. Accordingly, the bisquarternary tropeines produced by ~~we mostly through~~ quarternization with p-xylylene halides were of linear structures. Nador also synthesized certain bisquarternary tropanes which were stereoisomers on the N atom of the former. The procedure of synthesis was as follows: First, two molecules of nor-tropine ~~xxx~~ were reacted with one mol p-xylylene dibromide, thus securing the aralkyl group toward the 3-OH group. When this compound was quarternized with methyl halide, the methyl group had to be oriented toward the pyrrolidine part of the tropine ring system. Thus, ~~xxxxxxxxxxx~~ the whole molecule became ~~xxxxxxxx~~ sickle-shaped instead of becoming linear. This stereoisomer had about 1/40 of the curare-like action of the linear form. These examples illustrate the important role of steric structure in curare-like action. It seems to be conceivable that, for example, a sickle shaped structure cannot adequately attach itself to the receptors of the sarcolemma of ~~the~~ striated muscles. Besides these steric factors, another important feature of curare-like agents is their electron distribution around their N atoms.

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Remarkable difference exists between curare like bisquaternary tropeines and ganglionic blocking monoquaternary tropeines with regard to the pharmacologic potency of their stereoisomers: for example the curare like potency of bis-quaternary β (pseudo)-tropine derivatives is only 2-3 times inferior to that of the corresponding α-tropine derivatives whereas β-tropine is 13 times weaker on the autonomic ganglia than its α isomer. In the latter case the stereoisomerism, dependent upon the position of OH group, is of paramount importance. It is assumed therefore that this part of the molecule is being attached to the receptors. Regarding curare like action, however, it is the role of stereoisomerism on the N-atom which has crucial influence and is responsible for a 40 fold difference in potency between the N-stereoisomers. The cause of this major difference must be that the cationic N-groups are those which attach themselves to the receptors of the neuromuscular end plates.

Within the groups of ganglionic blocking tropeines the role of N-stereoisomerism is less marked. The action of these compounds is very weak on the postganglionic parasympathetic effector sites; in this regard no marked difference exists between the stereoisomers.

The atropine like action is dependent upon the presence of acidic groups such as tropic- or mandelic acids/ In 1904 Cushny found that l-hyosciamine with the l-tropic acid moiety is 40-100 times more potent in blocking the postganglionic parasympathetic effector sites than d-hyosciamine.

We believe that investigation of isomers may serve as a useful guide for characterizing the haptophore portion of drug molecules. It seems that the presence of those molecular groups play the most important role in the mechanism of action of certain drugs whose steric alterations exhibit the greatest influence on pharmacological activity.

the parasympathetic effector sites but the autonomic ganglia as well. Of this class of compounds Gastripon has shown therapeutic value. It differs from Manyl in that it is a tropic acid ester instead of being a mandelic acid derivative of tropine. According to the clinical observations it had a type of therapeutic action similar to those of Methantheline Propantheline Banthine and pro-Banthine. We assume that the therapeutic effectiveness of these agents is due to their depressant action on visceral reflexes. Gastropine has a N- stereoisomeric counterpart which proved to be much less effective. According to the studies of Decsi Neogastripon which is N(p-ethylbenzyl) atropinium bromide has stronger action on the parasympathetic effector sites and a weaker influence on the autonomic ganglia than Gastropin. It seems to be more selective for parasympathetic ganglia than Gastropin. Its oral adsorption is also better. Tropine esters of oxyaromatic acids usually have only blocking action on autonomic ganglia. But simple aromatic acid esters of tropine sometimes yield compounds with ganglionic stimulant action. In the latter group the most effective compound was N-417 which is the p-phenyl benzyl quaternary derivative of p-aminobenzoyltropine. According to the observations of Gyermek it is 50 times more effective in stimulating the sympathetic ganglia than nicotine. In these systematic studies it was demonstrated that the strength of the ganglionic blocking action is directly proportional to the size of the quaternizing group. Good examples are novatropine, N-239 and N-310. By changing the methyl groups in Novatropine by p- bromobenzyl group or p-phenylbenzyl groups the ganglionic blocking potency increased about 5 and 10 times respectively. On the other hand the size of the aromatic acid groups primarely influenced activity at the parasympathetic postganglionic receptor sites. Thus the substitution of tropic acid by the bulkier benzylic or xanthene 9- carboxylic acids results in compounds which are more potent, either in their tertiary amine or methyl quaternary forms than is atropine. (The same pneomena has also been observed by Wick and Engelhardt) N- 640 which is the methylquaternary derivative of tropine Xanthene 9-carboxylate has marked action at the parasympathetic postganglionic receptor sites and auto-

nomic ganglia as well. However the substitution of the N-methyl group of this compound by the large p-phenylbenzyl group (M-665) resulted, according to Gyorgy, in a decrease of anticholinergic potency.

Our aim to find compounds which can block selectively either the sympathetic or parasympathetic ganglia remained, so far, unsuccessful. In order to approach this objective we sythesized compounds with strong ganglionic blocking and weak atropine like action. Examples of this class of compounds are Gastripone and [redacted]

~~Nic~~astripone. Recently Nadori and Gyorgy succeeded in finding compounds which (~~besides the ganglia~~?) block the sympathetic (~~nerve endings~~?)

In the field of lobeline-type agents, our working hypothesis originated from the observations of V. Braun. He demonstrated that the pharmacophone group of the lobeline molecule can be transposed to the N-atom; thus compounds of considerably simpler structure could be obtained. This observation prompted our investigation with β-aminoketones. As a basic refernce compound we used diethylamino-3-phenyl-propanon-3.

In the large group of compounds synthesized we found few which produced acopolamine-like depression in cats and dogs. This was the reason why I suggested the exploration of the possible anti-Parkinson properties of these agents.

At that time, in 1953, it seemed to be the most suitable for these investigations to use the method of Bovet and Longo whereby the antagonism of the nicotine convulsions on rabbits is assessed. It was soon discovered that the reference compound and its piperidine analogue possess strong antinicotinic activities. These investigations have been continued by one of my talented collaborators, Dr. Porszasz. He found most suitable for therapeutic application the 1-piperidine-2-methyl-3-p-tolilpropanon-3. This compound which is known under the name of mydocalm, differs, for example, from panparnit in that it lacks the atropine-like activity; it does not produce dryness of the mouth, or tachy-cardia.

The results of the clinical tests corresponded with our expectations. This compound indeed ameliorated the increased muscle tone or rigidity produced by the disfunctioning of the extrapyramidal system. Part of its action was due to its inhibitory influence on polysynaptic reflexes. This action made it also useful as a muscle relaxant.

If the aryl group of the β-aminoketone type compound[5] is substituted by an alkyl radical the resulting compounds exhibit nicotine-like properties and act as antagonists to the actions of the former compounds. The explanation of these phenemonon is possible by considering the difference which exists between the electron attracting property of aryl groups which is present in one group of these compounds and the electron repellent nature of the alkyl groups existing in the other group.

According to Barlow in the acetylcholine molecule the keto group has polarizing effect, thus producing spots of different electron density. Besides other components such as steric factors and van der Waals forces, this polarization might play an important role in the attraction of molecules to receptor surfaces. Several potent nicotinic drugs are of dipolar character, and the attachment of these compounds might very well occur through hydrogen bonds between the keto groups and the receptor surface. Alycyclic groups also have electron repellent characteristics. If the keto group is a part of an alycyclic ring, a lobeline like respiratory stimulant action becomes predominant. A series of this type has been investigated by Porszasz, and one of the compounds: 1-piperidinomethyl cyclohexan-2-on has been clinically tested and marketed under the

the name "spiractin". Unlike lobeline it had longer action and did not produce acute cardiac complications. Of the aminoketones with condensed ring systems those having fully hydrated rings possess nicotine like properties. If, however, only one ring is being hydrogenated as it is in the case of N-86 the compound becomes an adrenolytic agent and also decreases basal metabolism. This latter action is mediated through its depressant influence on sympathetic centers of the hypothalamus. This is indicated by its blocking action against the metabolic effect of amphetamine. If two alkyl groups are attached to the aromatic ring system as in N-702 the adrenolytic action markedly decreases and a tranquilizing action of the same intensity as that of chlorpromazine appears. This action was also discovered by one of my pupils Dr. Knoll.

In the preceeding presentation I intended to shortly describe those investigations to which I have given only the initial impetus. A great deal of the merit must go to my excellent and industrious pupils and coworkers for their outstanding performance throughout the years of work. Amongst them I would like to mention the names of the chemist Dr. Nador and the pharmacologists Drs. Gyermek, Porszasz, Knoll and Gyorgy. They synthesized and investigated almost one thousand new compounds. Again it became evident that valuable new drugs could only be developed through determination and systematic pharmacological research. Furthermore, our studies call upon the importance of stereochemical features, role of steric factors and particularely the significance of the changes in electron density.

I believe that further development in drug research and an avolution from its present, greatly empirical stage can be expected through the advancement of biochemical sciences: a more thorough knowledge is required for the understanding of the function of those enzyme systems which may act as drug receptors. Development of new theories in organic chemistry will certainly come. Their application in pharmacology will also be of great importance for the future success of drug research.